Ethical and Regulatory Aspects of Human Subjects Research

Department of Clinical Bioethics
Wednesday mornings 8:30 a.m. – 11:30 a.m.
Building 10/ Lipsett Auditorium
October 12 to November 30, 2005
SYLLABUS WITH READINGS

COURSE READINGS

1. Course Textbook:

Emanuel E, R. Crouch, J. Arras, J. Moreno, and C. Grady. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore: Johns Hopkins University Press 2003. (Available from the FAES bookstore)

2. Supplemental readings on course CD

READINGS BY SESSION

<u>October 12, 2005- Session 1: History of and Framework for Human Subject Research</u>

8:30-8:45 Pre-test
Introduction to the goals and structure of the course

8:45-9:20 Framework for the Ethics of Research with Human Subjects
Ezekiel Emanuel, M.D. Ph.D.
Chair, Department of Clinical Bioethics, NIH

9:20-9:30 Discussion

READINGS:
CD
Emanuel E, Wendler D, Grady C. What makes Clinical Research Ethical? *JAMA* 283 (20) 2701-2711, 2000

Emanuel E, Wendler D, Killen J, Grady C. What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research *J Inf Dis* 2004; 189:930-7.

9:30-10:10 Scandals and Tragedies: Beecher, Tuskegee, Willowbrook and the Rest
John Arras, Ph.D.
Porterfield Professor of Biomedical Ethics, University of Virginia

10:10-10:20 Discussion

READINGS:
<u>Textbook Part 1,</u> Intro and
Chapter 1. Faden et al. "US medical researchers, the Nuremberg Doctors Trial, and the Nuremberg Code.".
Chapter 2. Katz et al . "The Jewish chronic disease case,"
Chapter 3. Beecher, H. "Ethics and clinical research."

Chapter 4. Brandt, A.. "Racism and Research: The case of the Tuskegee Syphilis Study.".

10:20-10:40 **Break**

10:40-11:20 Conflicts of Interest
Cary Gross MD
Yale University School of Medicine

11:20-11:30 Discussion

READINGS:
Textbook- Part VIII, Intro and
Chapter 72. Thompson D. "Understanding Financial Conflicts of Interest"
Chapter 74. Brody B. Conflicts of Interest and the Validity of Clinical trials.
Chapter 75. Martin, JB and Kasper, DL. "In whose best interest? Breaching the academic-industrial wall."

CD
Beckelman J, Li Y, Gross C. Scope and Impact of Financial Conflicts of Interest in Biomedical Research. *JAMA* 2003; 289: 464-465.
Bodenheimer, T. "Uneasy alliance. Clinical investigators and the pharmaceutical industry." *NEJM;* 2000; 342(20):1539-1544.
Lexchin J, Bero L, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review**.** *BMJ* 2003; 326: 1167-1170

October 19, 2005 **Session 2 – Codes of Research Ethics, IRB Review, and Subject Selection**

8:30-9:10 Do the Codes Apply to My Research Protocol? Nuremberg, Helsinki, the Belmont Report, CIOMS, and the Common Rule
Christine Grady, Ph.D.
Head, Section on Research Ethics, Department of Clinical Bioethics, NIH

9:10-9:20 Discussion

READINGS:
Textbook Part II, Intro and
Chapter 5. The Nuremberg Code
Chapter 6. The Declaration of Helsinki
Chapter 7. The Belmont Report

9:20-10:05 The Purpose and Function of IRBs: Successes and current challenges
Dale Hammerschmidt, M.D.
Director of Education in Human Subjects Protection, University of Minnesota

10:05-10:15 Discussion

READINGS:
Textbook - Part II and X

Chapter 8. The Common Rule
Chapter 85. Edgar H, Rothman D. "The Institutional Review Board and Beyond: Future challenges to the ethics of human experimentation."

CD
Emanuel E, Wood A, Fleischman A, Bowen A, Getz K, Grady C, Levine C, Hammerschmidt D, Faden R, Eckenwiler L, Tucker C, Sugarman J. Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals. *Annals of Internal Medicine* 2004; 141(4):282-291.

10:15-10:35 **Break**

10:35-11:20 Fair Subject Selection
Dave Wendler PhD
Department of Clinical Bioethics/NIH

READINGS:
Textbook- Part IV
Chapter 22. Jonas, Hans. "Philosophical reflections on experimenting with human subjects."
Chapter 23, Heyd D. "Experimentation on trial: Why should one take part in medical research"

CD
Wendler D. When should 'riskier' subjects be excluded from research? *Kennedy Institute of Ethics Journal* 1998; 8:307-327.

October 26, 2005 Session 3 – Ethics of Recruitment/payment and Randomized controlled trials

8:30-9:10 Recruitment and payment of research subjects
Neal Dickert
Johns Hopkins University School of Medicine

9:10- 9:20 Discussion

READINGS:
Textbook- Part IV. Section 3
Chapter 27, Dickert N, Grady C. "What's the price of a research subject"?
Chapter 28, Lemmens T, Elliott C. "Justice for the professional guinea pig"
Chapter 29, McNeill P. "Paying people to participate: why not?"

9:20- 10:00 Ethics of Randomized Clinical Trials: Clinical Equipoise
Robert Truog, M.D.
Professor of Anesthesiology & Medical Ethics, Harvard Medical School

10:00-10:10 Discussion
READINGS:
Textbook Part III, Intro Section One, and
Chapter 11. Levine R. "Research and practice,"

Chapter 12. Freedman B et al. Demarcating research and treatment: A systematic approach for the analysis of clinical research
Intro Section Two,
Chapter 13. Hellman S, Hellman DS. "Of mice but not men: Problems of the randomized clinical trial."
Chapter 14. Freedman B. "Equipoise and the ethics of clinical research."
Chapter 15. Truog R. "Randomized Controlled Trials: Lessons from ECMO."

10:20- 10:30 Break

10:30- 11:30 Mock IRB
Before this session please read the protocol provided to you

November 2, 2005 **Session 4 – Ethical Issues in Research with children, Phase 1 oncology studies, and placebo controlled trials**

8:30-9:10 Ethics of Placebo Controlled Trials
Frank Miller PhD
Department of Clinical Bioethics/NIH

9:10-9:20 Discussion

READINGS:
Textbook- Part III, Intro Section Three, and
Chapter 16. Rothman K, Michels K. "The continuing unethical use of placebo controls."
Chapter 17. Freedman B. "Placebo-Controlled trials and the logic of clinical purpose." Chapter 18. Temple R, Ellenberg S. "Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments, Part 1: Ethical and Scientific Issues."
Chapter 19. Emanuel EJ, Miller FG. "The Ethics of Placebo-Controlled Trials – A Middle Ground."

CD
Miller F, Brody H. A critique of clinical equipoise: the therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003; 33(3): 19-28.

9:20-10:05 Ethics of Research with Children
Alan Fleischman MD
National Institute of Child Health and Development
Senior Vice President, New York Academy of Medicine

10:05-10: 15 Discussion

READINGS:
Textbook, Part VI
Chapter 41. Tauer C. "The NIH trials of growth hormone for short stature."
Chapter 43. Leikin S. "Minors assent, consent, or dissent to medical research."
Chapter 42. Freedman B, Fuks A, Weijer C. "*In loco parentis*: Minimal risk as an ethical threshold for research upon children,"

CD

Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do IRBs apply the federal risk and benefit standards for pediatric research? *JAMA*. 2004; 291:476-482.

10:15- 10:35 Break

10:35- 11:20 Ethics of Phase I Oncology Research
Manish Agrawal, M.D.
National Cancer Institute

11:20-11:30 Discussion

READINGS:
Textbook, Part III
Chapter 20. Lipsett MB. "On the nature and ethics of Phase I Clinical Trials of Cancer Chemotherapies."
Chapter 21. Annas GJ. "The changing landscape of human experimentation: Nuremberg, Helsinki, and Beyond."

CD
Agrawal M, Emanuel E. "Ethics of Phase 1 Oncology Studies: Reexamining the Arguments and Data." *JAMA* 2003; 290(8): 1075-1082.
Daugherty C et al. "Learning from our patients: One participant's impact on clinical trial research and informed consent." *Annals of Internal Medicine*, 1997;126: 892-897.

November 9.2005 **Session 5 –Informed consent and research with those who have impaired capacity to consent**

8:30-9:10 Informed consent: the ideal and the reality
Christine Grady RN PhD
Department of Clinical Bioethics/NIH

9:10-9:20 Discussion

READINGS:
Textbook, Part V, Intro and
Chapter 30 Levine, R. Consent issues in human research
Chapter 31 Inglefinger, F. Informed (but uneducated) consent
Chapter 32 Freedman, B. A moral theory of informed consent
Chapter 35 Subject Interview Study
Chapter 36. Appelbaum P, Roth L., Lidz C, et al. "False hopes and best data: Consent to research and the therapeutic misconception."

Also see OSHR, "Guidelines for writing informed consent documents," from **http://helix.nih.gov:8001/oshr/info/finfo_6.php**, 1997.

CD:
Sachs GA, Hougham GW, Sugarman J, Agre P, Broome ME, Geller G, Kass N, Kodish E, Mintz J, Roberts LW, Sankar P, Siminoff LA, Sorenson J, Weiss A. Conducting empirical research on informed consent: challenges and questions. *IRB*. 2003 Sep-Oct;Suppl 25(5):S4-S10.

Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA*. 2004 Oct 6;292(13):1593-601.

9:20-10:00 Research Involving Persons at Risk for Impaired Decision-Making
Donald Rosenstein, M.D.
Chief, Psychiatry Consult-Liaison Service
Clinical Director, NIMH

10:00-10:10 Discussion

READINGS:
Textbook Part VI

Chapter 38. National Bioethics Advisory Commission, excerpts from "Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity"

CD
Carpenter WT, Gold JM, Lahti AC, et al. "Decisional Capacity for Informed Consent in Schizophrenia Research." *Archives of General Psychiatry,* 2000; 57:533-538.
Applebaum P. "Involving Decisionally Impaired Subjects in Research - The Need for Legislation." *AM J Geriatric Psychiatry,* 2002; 10(2):120-124.
Cassaret D. Assessing decision making capacity in the setting of palliative care research, Journal of Pain and Symptom Management 2003; 23(4):36-
Kim Scott YH, Karlawish Jason HT, Caine Eric D. "Current State of Research on Decision-Making Competence of Cognitively Impaired Elderly Persons." *Am J Geriatric Psychiatry*, 2002; 10(2):151-165.
Chen DT, Miller FG, Rosenstein DL. "Enrolling Decisionally Impaired Adults in Clinical Research." *Medical Care*, 2002, Vol. 40(9) 20-29.
Misra S, Ganzini L. Capacity to consent to research among patients with bipolar disorder. Journal of Affective Disorders. 2004; 80:115-123

10:10-10:25 Break

10:25- 11:30 Participant Panel

November 16, 2005 **Session 6 – Ethical Issues in International Research**

8:30-9:15 Exploitation
Alan Wertheimer PhD
Visiting Scholar Department of Clinical Bioethics/NIH, and University of Vermont
9:15- 9:25 Discussion

READINGS:
Textbook, Part VII
Chapter 65. Lurie P and Wolfe S. "Unethical Trials Of Interventions To Reduce Perinatal Transmission Of The Human Immunodeficiency Virus In Developing Countries"
Chapter 66. Annas G and Grodin M. "Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa"

CD
Wertheimer A. Chapter 1 "Overview" in Wertheimer A. Exploitation. Princeton, NJ: Princeton University Press, 1996. pages 3-34.

9:25- 10: 10 Fair benefits, ancillary care, and post trial considerations
Reidar Lie MD PhD
Department of Clinical Bioethics

10:10-10:20 Discussion

READINGS:
CD
Participants in the 2001 conference on Ethical Aspects of Research in Developing Countries. Moral Standards for Research in Developing countries. From "reasonable availability" to "fair benefits" *Hastings Center Report* 2004; 34(3): 17-27.
Ananworanich J, Cheunyam T, Teeratakulpisarn S, Boyd M, Ruxrungtham K, Lange J, Cooper D, Phanuphak P. Creation of a drug fund for post-clinical trial access to antiretrovirals. *Lancet* 2004; 364:101-2
Belsky L, Richardson H. Medical researchers' ancillary clinical care responsibilities. *Brit Med J*. 2004 Jun 19;328(7454):1494-6.
C. Slack, et al., "Provision of HIV treatment in HIV preventative vaccine trials: a developing country perspective," *Social Science & Medicine*, 2004.
Lie R, Emanuel E, Grady C, Wendler D. The Standard of Care Debate: The Declaration of Helsinki versus the International Consensus Opinion. *Journal of Medical Ethics* 2004; 30:190-193

10:20- 10:40 Break

10::40- 11:20 International Research: ethical Issues in the field
Elizabeth Higgs MD
National Institute of Allergy and Infectious Diseases

11:20- 11:30 Discussion

November 23, 2005 ***HAPPY THANKSGIVING***

November 30, 2005 **Session 7 – Genetics, Stored Tissue, and HIPAA**

8:30-9:10 Ethical Issues in Genetics Research
Benjamin Wilfond, M.D.
Medical Genetics Branch, NHGRI
Head, Section on Ethics and Genetics, Department of Clinical Bioethics

9:10-9:20 Discussion

READINGS:
Textbook Part VII
Chapters 48 Glass, K, et al. Structuring the review of human genetics protocols: gene localization and identification studies

Chapter 49 Glass, K, et al. Structuring the review of human genetics protocols, part II: diagnostic and screening studies
Chapter 50 Glass, K, et al. Structuring the review of human genetics protocols, part III: gene therapy studies

CD
Juengst, E. "Human Genetics '98: Ethical Issues in Genetics: Group identify and human diversity: Keeping biology straight from culture." *American Journal of Human Genetics*, 1988; 63: 673-677.
Botkin, J et al. "Privacy and confidentiality in the Publication of Pedigrees: A survey of investigators and biomedical journals." *JAMA*, 1998; 279(22): 1808-1812.
Hull SC, Glanz K, Steffen A, Wilfond B. Recruitment approaches for family studies: attitudes of index patients and their relatives. *IRB*. 2004;26(4):12-7.

9:20-10:00 **Case Discussion**

Please read the case provided to you.

10:00- 10:20 **Break**

10: 20-11:00 Ethical Issues in the Use of Stored Tissue
Sara Chandros Hull, Ph.D.
Bioethics Research Section, Medical Ethics Branch, NHGRI

11:00- 11:10 Discussion

READINGS:
Textbook, Part VII.
Chapter 53. Wright, E, et al. "Informed consent for genetic research on stored tissue samples."
Chapter 54. Merz, J et al. "Use of human tissues in research: Clarifying clinician and researcher roles and information flows."

CD
National Bioethics Advisory Commission. "Research Involving Human Biological Materials: Ethical Issues and Policy Guidance – Executive Summary," August 1999**.**
Lavori PW, Krause-Steinrauf H, Brophy M, et al. "Principles, organization, and operation of a DNA bank for clinical trials: a Department of Veterans Affairs cooperative study." *Controlled Clinical Trials,* 2002; 23(3):222-39.
Hull S, Gooding H, Klein A, Warshauer- Baker E, Metosky S, Wilfond BS. Genetic Research Involving Human Biological Materials: A need to tailor consent forms. *IRB*. 2004; 26 (3): 1-7